Testimony
Before the Special Committee on Aging
United States Senate

NIH's Biomedical Research Response to Influenza

Statement of

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For Release on Delivery
Expected at 10:00AM
Tuesday, September 28, 2004

Introduction

Mr. Chairman and Members of the Committee, thank you for the opportunity to discuss with you the role of the National Institutes of Health (NIH) in combating influenza and other emerging and re-emerging infectious disease threats. Responding effectively to the challenges posed by diseases such as influenza, SARS, West Nile virus, or HIV requires a multi-faceted, coordinated and focused approach with close collaboration between public health authorities, health care delivery systems, the pharmaceutical industry, and the biomedical research community. The National Institute of Allergy and Infectious Diseases (NIAID), a component of NIH, is the lead Federal agency for conducting, supporting, and coordinating research on influenza and other infectious diseases. As such, NIAID plays a key role in our national effort to prepare for and to respond robustly to the threat of influenza and other emerging infectious diseases.

Emerging and Re-emerging Infectious Diseases

Infectious diseases have afflicted humanity since ancient times, and they will continue to confront us as long as man and microbes co-exist. Unfortunately, the viruses, bacteria, and parasites that cause infectious diseases do not remain static, but continually and dramatically change over time as new pathogens emerge and as familiar ones (such as influenza) re-emerge with new properties or in unfamiliar settings. Such emerging and re-emerging infections have shaped the course of human history while causing incalculable misery and death.

Our ability to respond effectively to new infectious disease threats, whether they are emerging, re-emerging, or deliberately introduced, involves many different kinds of activities and many different organizations. From a public health perspective, surveillance and response are the key elements in controlling emerging and re-emerging infections and depend upon rapid detection and containment of pathogens in populations and the environment. Globally, such efforts are coordinated by the World Health Organization (WHO). In the United States, such efforts are led by the Centers for Disease Control and Prevention (CDC), which along with state and local health departments and other agencies recently have made significant strides in national disease surveillance and response capacity. Physicians, nurses, other health care workers and hospitals also must be integrated to respond in a coordinated manner to an outbreak, and the pharmaceutical industry must be fully engaged to develop and manufacture needed diagnostic tools, therapeutics, and vaccines. Within the Department of Health and Human Services (HHS), NIH, CDC, the Food and Drug Administration (FDA), and other agencies all have distinct but complementary roles to play, and have a long history of cooperation. The NIH concentrates on a strong and focused research program that is critical to preventing and controlling these infectious disease threats.

The conduct, support, and coordination of basic, translational, and applied infectious disease research is the primary responsibility of NIAID. First and foremost, NIAID supports basic and clinical research, which is needed to understand how pathogens

cause disease. These research efforts include understanding how microbes replicate, how disease spreads, and what factors lead them to cause serious illness or death. Of particular importance is to understand how the body's protective mechanisms, i.e. the immune system, protect against the devastating effects of microbial invaders. In addition, NIAID works closely with academic and industrial partners to translate basic and clinical research findings into new diagnostic tools, therapeutics, and vaccines. This translational and applied research effort also involves close coordination with FDA, CDC, and other Federal agencies to ensure that new countermeasures move as efficiently as possible from the laboratory into general use.

Influenza Research Activities at NIAID

Influenza is a classic example of a re-emerging disease; it is not a new disease, but it continually changes. In most years, influenza viruses that typically infect humans globally undergo small changes in the properties of their surface proteins. If enough of these changes accumulate, the virus is able to escape the human immune response that resulted from prior exposure to influenza viruses or vaccination. This is referred to as "antigenic drift" and it is the basis of well-recognized patterns of influenza disease that occur every year and cause significant mortality and morbidity. According to new estimates, influenza infections are estimated to result in an average of 36,000 deaths and over 200,000 hospitalizations each year in the United States, and the WHO estimates that the annual average number of deaths worldwide is approximately 500,000. One of the population groups at risk of the serious complications of influenza

is the group over 65 years of age. The CDC recommends that this age group be vaccinated against influenza each year, and the HHS has set a goal of 90% vaccination coverage for them. However, we know that currently only two-thirds of this group is vaccinated each year.

Although only three types of influenza viruses routinely circulate among humans, all known influenza A subtypes are endemic in the gastrointestinal tract of wild ducks. Because the replication machinery of the influenza virus is error prone, as the virus multiplies, avian influenza viruses can emerge that may be able to jump species into domestic poultry, farm animals such as pigs, and humans. When an influenza virus jumps species from an animal such as a chicken to a human, it usually is a "dead end" infection in that the virus cannot readily transmit further from human to human. Avian influenza viruses made the jump directly from birds to humans in 1997, but because the virus did not acquire the ability to spread from human to human, only a limited number of deaths (6 out of 18 confirmed cases) occurred. Currently, H5N1 avian influenza viruses in Vietnam and Thailand also have made the jump directly from birds to humans and have resulted in deaths of 28 out of 39 confirmed cases (as of September 7) representing a 72% mortality rate. The fear is that the avian H5N1 and a commonly circulating human influenza virus such as H3N2 might recombine if they were to simultaneously co-infect a person, resulting in the global spread of a new, deadly influenza virus that can be spread among humans and to which the majority of the world will be susceptible, referred to as a pandemic strain. This type of significant change in

the antigenic makeup of the virus, which can result in a pandemic, is referred to as an "antigenic shift".

Deadly pandemics are known to have occurred in 1918, 1957, and 1968. The pandemic that occurred in 1918-1919 after an antigenic shift killed 20-40 million people worldwide, including more than half a million in the United States. The pandemics that occurred following other shifts in the virus in 1957 and 1968 killed approximately 2 million and 700,000 people worldwide, respectively. This explains our current high level of concern about the appearance of new forms of virulent H5N1 avian influenza viruses in Asia, which could subsequently recombine with human influenza viruses and result in another pandemic. Given the poor condition of public health systems in many underdeveloped regions and the speed of modern air travel, the consequences of such an event, should it result in an influenza pandemic, would be severe.

The overall goal of the Influenza Program at the NIAID is to support research that leads to more effective approaches for controlling influenza virus infections. This program has two major components, both of which are specified in the nation's draft Pandemic Influenza Preparedness and Response Plan. The first component reflects longstanding programs for interpandemic influenza—research to understand the pathogenesis, transmissibility, evolution, epidemiology, and the immune response to influenza viruses. These interpandemic research areas include:

- **Basic Research.** NIAID supports many basic research projects aimed at understanding how the influenza virus replicates, interacts with the host, stimulates an immune response and evolves into new strains. Results from these studies provide the information needed for the design of new antiviral drugs, diagnostics, and vaccines.

- **Antiviral Drugs.** NIAID currently supports the identification, development and evaluation of new antivirals against influenza including the screening of new drug candidates to see if they are active against the virus both in laboratory cells and in animals. We also are developing novel broad-spectrum therapeutics intended to work against many influenza virus strains; some of these target viral entry into human cells, while others specifically attack and degrade the viral genome. Development and evaluation of a combination antiviral regimen against potential pandemic influenza strains is also now under way.

- **Diagnostics.** NIAID supports the development of rapid, ultra-sensitive devices to detect influenza virus infection. Although we are at an early stage of development, these devices will allow detection of newly emerging viral mutants and discrimination between different antigenic sub-types. Other diagnostics in development will have the ability to discriminate between influenza and other pathogens that cause so-called

"flu-like symptoms", such as SARS. A more rapid identification of the disease-causing agent will allow for faster and more effective treatment and control measures.

- **Vaccines.** Because influenza is so easily transmitted, effective vaccines are essential to the control of annual influenza epidemics. The current egg-based system used to produce licensed influenza vaccines—despite being reliable for more than 50 years—can be improved. Limitations of the current system include: (1) a lengthy manufacturing process; (2) the need to select which virus strains will be in the vaccine at least six months in advance of the influenza season; (3) the need to produce enough new influenza vaccine each year to meet the continually increasing demand (about 100 million doses in 2004); and (4) the requirement of hundreds of millions of fertilized chicken eggs to manufacture the vaccine. This early decision about which strains to include in the influenza vaccine will not always be correct, and the long lead time required to produce the vaccine makes mid-stream corrective action impossible. Additional limitations could include allergenicity of eggs in some individuals and inability to use eggs for propagation of viruses lethal to chickens.

NIAID is currently supporting a number of research projects aimed at developing influenza vaccines that can be manufactured more rapidly, are more broadly cross-protective, and are more effective. The use of reverse genetics—a tool developed by NIAID-supported scientists—holds the promise for more rapid generation of high-yielding vaccine candidates that match the anticipated epidemic strain. Reverse genetics also can be used to turn highly pathogenic influenza viruses into vaccine candidates more suitable for vaccine manufacturing by removing or modifying certain virulence gene sequences; laboratories around the world have used this technique to prepare vaccine candidates against the H5N1 viruses that emerged in Asia in 2004.

NIAID also supports the development of new influenza vaccine technologies. Recently, NIAID supported a Phase II clinical trial in older adults of a new influenza vaccine produced in a cell culture system, as an alternative to manufacturing the vaccine in eggs. The results of this trial suggest that this new vaccine approach could be a viable alternative to the traditional egg-based influenza vaccine. Other studies have focused on the development of broadly protective vaccines that induce protection against multiple strains of influenza and, therefore, do not need to be updated yearly.

NIAID is supporting studies to improve the effectiveness of current inactivated vaccines in elderly individuals, the population that frequently accounts for up to 90% of the influenza deaths each year in the United States. Although vaccination in this population is very effective in preventing severe illness, secondary complications, and death, we have seen that elderly individuals are protected less effectively by vaccination than younger individuals. NIAID has recently supported a clinical trial in the elderly to evaluate doses of the inactivated vaccine with increased antigen content. The results of this trial suggest that increased doses of vaccine in this population result in a higher level of protective antibodies against influenza virus. Another study is currently being supported to evaluate the effect of exercise on the immune response to influenza vaccination in older adults. The results suggest that older adults who participate in regular exercise programs had a higher antibody response to the vaccine than did their sedentary counterparts. NIAID has recently supported a research grant to elucidate why the elderly respond less effectively to vaccination and to determine if a novel booster vaccination strategy would improve efficacy in the elderly.

Because NIAID has had remarkable success in the past with groundbreaking vaccine research—including advances that led to hepatitis B, *Haemophilus influenzae b*, pneumoccocal pneumonia, and acellular

pertussis vaccines, as well as the new live attenuated intranasal influenza vaccine approved by the FDA last year—I am confident that one of the approaches we are pursuing also will lead to a useful, “next-generation” influenza vaccine that can easily be adapted to emerging influenza strains.

- **Surveillance and Epidemiology.** The threat from influenza, like virtually all emerging and re-emerging infectious disease threats, is global in scope. For this reason, NIAID has expanded its activities in other countries in recent years. Through a contract for pandemic influenza preparedness, NIAID supports a long-standing program in Hong Kong to detect the emergence of influenza viruses with pandemic potential in animals. Under this program, Dr. Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, leads a group that detected the re-emergence of highly pathogenic H5N1 avian strains in this area in 2002 and 2003, and was instrumental in the early detection and characterization of the SARS coronavirus in 2003. This underscores the concept that research on one type of infectious disease often supports or can be applied to research on the other types of infectious diseases, whether newly emerging, re-emerging, or deliberately introduced.

The second component of NIAID’s Influenza Program is geared to address the emergence of influenza viruses with pandemic potential in humans. The U.S. Pandemic

Influenza Preparedness and Response Plan describes specific roles for NIAID, should a pandemic influenza strain emerge and a Pandemic Alert be declared. Foremost among these responsibilities is to help develop and produce an effective vaccine as rapidly as possible. Under this plan, NIAID would assist in the characterization of the newly emerging influenza strain, create vaccine candidates, develop investigational lots of candidates, and produce and distribute research reagents for use by vaccine researchers in academic and pharmaceutical industry laboratories. NIAID would also work with industry to produce and conduct clinical studies on vaccine candidates. NIAID-supported scientists will also evaluate the susceptibility of the newly emerging virus to the currently available influenza drugs and new drug candidates. NIAID has already begun to implement this carefully-planned process in response to the avian influenza outbreak in Southeast Asia.

NIAID utilized reverse genetics to generate a reference strain that has the antigenic characteristics on the H5N1 avian influenza strain, but is safe for researchers to work with in the lab. NIAID has provided the reference strain to currently licensed influenza vaccine manufacturers, Aventis Pasteur, Inc. and Chiron Corporation. Under contract, both manufacturers are developing pilot lots of inactivated H5N1 vaccine. NIAID will test this vaccine for safety and immunogenicity in humans; it is planned that one of the groups in the study will be older adults. HHS recently awarded a contract to Aventis to manufacture and store 2 million doses of this vaccine. These actions are critical steps which will help prepare the nation to respond to a pandemic influenza outbreak. All of

this work is done in close coordination with CDC, FDA, and WHO. This coordination is needed if a safe and effective vaccine is to be available to the public as soon as possible.

Conclusion

Mr. Chairman, thank you again for inviting me to discuss NIH's efforts to address the threat of influenza. In addition to the significant toll exacted by influenza each year in the United States, the risk of pandemic influenza is significant and the consequences could be very serious. Influenza, however, is one among many ever-changing infectious disease threats confronting our nation and the world that have serious adverse health and economic impact. Fortunately, much of what we learn from the study of one pathogen can often be applied to others. As I have described for you today, NIAID, as the lead Federal agency for infectious diseases research, constantly strives to improve its ability to respond to any infectious disease threat.

I would be pleased to answer your questions.